

Supplementary Information:

- Table S1. Retrogenix array: ID of spotted genes encoding human plasma membrane proteins
- Table S2. Recombinant proteins of the study, primers and production method
- Table S3. Binding of DC8 expressing parasites to endothelial cells
- Table S4. Data pertaining to the clinical parasite isolates tested for EPCR binding
- Fig. S1. Model of EPCR mediated parasite binding to endothelial cells leading to severe malaria
- Fig. S2. Additional SPR sensorgrams
- Fig. S3. *Var/PfEMP1* expression profiles of FCR3/IT and 3D7 parasite lines
- Fig. S4. *Var* expression profiles of parasite isolates 1965 and 1983
- Fig. S5. Effect of anti EPCR monoclonal antibody RCR-252 on FCR3 IT4VAR20 parasite binding to brain endothelial cells
- Fig. S6. Microscopy pictures of PfEMP1 expression and infected erythrocyte binding

Table S1. Retrogenix array: ID of spotted genes encoding human plasma membrane proteins

| AAK1 | ADRB1 | AP1S1 | ATP2B3 | BST2 | CAPNS2 | CD1B | CD96 | CHRNA3 | CNTFR | CXCR1 | DPP4 | EFR3A | ESYT2 |
|-----------|-----------|----------|----------|---------|----------|---------|----------|---------|---------|---------|--------|----------|---------|
| AAMP | ADRB2 | AP1S3 | ATP2B4 | BTC | CAPRIN1 | CD1E | CD97 | CHRNA4 | CNTN4 | CXCR2 | DRD1 | EGFLAM | EVL |
| ABCA8 | ADRB2 | AP2A1 | ATP4A | BTC | CASP3 | CD2 | CD99 | CHRNA5 | CNTNAP2 | CXCR2 | DRD1 | EGFR | EWSR1 |
| ABCB6 | ADRBK1 | AP2A2 | ATP5A1 | BTK | CASR | CD200 | CD99L2 | CHRNA6 | CNTNAP3 | CXCR3 | DRD2 | EHD2 | EZR |
| ABCC10 | ADRM1 | AP2B1 | ATP5B | BTN1A1 | CAT | CD200 | CD99L2 | CHRNA9 | COL17A1 | CXCR3 | DRD2 | EHD3 | FI0 |
| ABCG1 | AFAP1 | AP2M1 | ATP5O | BTN2A1 | CATSPER1 | CD200R1 | CD99L2 | CHRNBI | COL1A1 | CXCR4 | DRD3 | EIF2B1 | F11R |
| ABCG1 | AGER | AP4M1 | ATP6AP2 | C1QBP | CATSPER2 | CD209 | CDC42 | CHRNBI | COL1A2 | CXCR4 | DRD3 | ELTD1 | F11R |
| ABCG2 | AGTR1 | APBB1 | ATP6V0A1 | C1QBP | CAV1 | CD24 | CDC42EP1 | CHRNBI | COL23A1 | CXCR6 | DRD3 | EMCN | F2 |
| ABI2 | AGTR1 | APBB1IP | ATP6V0A2 | C3AR1 | CAV1 | CD244 | CDC42EP1 | CHRND | COL25A1 | CXCR6 | DRD3 | EMPI | F2R |
| ABRA | AGTR1 | APCDD1 | ATP6V0D1 | C3AR1 | CAV2 | CD247 | CDC42EP2 | CIB1 | COL6A1 | CXCR6 | DRD3 | EMR1 | F2R |
| ACCN3 | AGTR2 | APH1A | ATP6V1B1 | C5AR1 | CBL | CD27 | CDCP1 | CLCA1 | COL6A2 | CXCR7 | DRD3 | EMR2 | F2RL1 |
| ACCN4 | AGTRL1 | APH1B | ATP6V1B2 | C5AR1 | CBLN1 | CD28 | CDCP1 | CLCA2 | COLQ | CXorf61 | DRD3 | EMR3 | F2RL1 |
| ACCN5 | AIF1 | APH1B | ATP6V1C1 | C5AR1 | CBLN3 | CD300A | CDH1 | CLDN1 | COMT | CYBA | DRD3 | EMR3 | F2RL1 |
| ACCN5 | AIF1L | APH1B | ATP6V1E1 | C6 | CBLN4 | CD300C | CDH10 | CLDN10 | COMT | CYBB | DRD3 | ENAH | F2RL2 |
| ACE | AIF1L | APLNR | ATP6V1G1 | C6orf25 | CCDC70 | CD300E | CDH11 | CLDN11 | CPE | CYSLTR1 | DRD4 | ENG | F2RL2 |
| ACE2 | AIF1L | APLP1 | ATP6V1G3 | C7 | CCDC8 | CD300LB | CDH12 | CLDN12 | CPEB1 | CYSLTR1 | DRD4 | ENO1 | F2RL3 |
| ACHE | AIFM3 | APLP2 | ATP6V1H | C8A | CCKAR | CD300LD | CDH13 | CLDN14 | CPLX3 | CYSLTR2 | DRD4 | ENO1 | F3 |
| ACTL6A | AJAPI | APOA1 | AVPR1A | C8B | CCKBR | CD300LF | CDH15 | CLDN14 | CPM | CYSLTR2 | DRD4 | ENO2 | F5 |
| ACTN2 | AKAP5 | APOE | AVPR1B | C8G | CCKBR | CD300LG | CDH16 | CLDN15 | CRB2 | CYSLTR3 | DRD5 | ENOX1 | F5 |
| ACTR3 | AKAP7 | APOLD1 | AVPR2 | C9 | CCKBR | CD33 | CDH18 | CLDN16 | CRCP | CYSLTR4 | DRD5 | ENPP1 | F5 |
| ACVR1 | AKT1 | APOM | AVPR2 | C9orf11 | CCNY | CD34 | CDH19 | CLDN17 | CRFR2 | CYTH1 | DRD6 | ENPP2 | F5 |
| ACVR1B | AKT2 | APP | AXL | CA11 | CCNY | CD36 | CDH2 | CLDN18 | CRHR1 | CYTH2 | DSC1 | ENPP3 | F7 |
| ACVR2A | AKTIP | AQP1 | AZGP1 | CA2 | CCR1 | CD38 | CDH26 | CLDN19 | CRHR1 | CYTH3 | DSG1 | ENPP5 | F8 |
| ACVR2B | ALCAM | AQP2 | B2M | CA4 | CCR1 | CD3D | CDH29 | CLDN2 | CRHR1 | DAB2 | DSG1 | ENPP6 | F9 |
| ACVRL1 | ALDOB | AQP5 | B3GNT3 | CA9 | CCR1 | CD3E | CDH3 | CLDN20 | CRHR2 | DAG1 | DTNBP1 | ENTPD1 | FADD |
| ACY3 | ALG10B | AQP7 | B4GALT1 | CABP1 | CCR10 | CD4 | CDH6 | CLDN25 | CRIM1 | DAPP1 | DUOX2 | ENTPD3 | FADS2 |
| ADA | ALK | AQP8 | BACE1 | CABP2 | CCR2 | CD40 | CDH7 | CLDN3 | CRIP1 | DARC | DUSP3 | ENTPD8 | FAF1 |
| ADAM11 | ALOX12 | AQP9 | BAII | CABP7 | CCR2 | CD40LG | CDH8 | CLDN4 | CRK | DARC | DYNLL1 | ENTPD8 | FAIM2 |
| ADAM12 | ALOX5 | ARC | BAIAP2 | CACNB1 | CCR2 | CD44 | CDHR1 | CLDN5 | CRLF2 | DARC | DYNLL2 | EPB41 | FAM127A |
| ADAM15 | ALPI | ARF1 | BAMBI | CACNB3 | CCR2 | CD46 | CDHR3 | CLDN6 | CRTAM | DCBLD2 | EBAG9 | EPB41L1 | FAM57A |
| ADAM2 | ALPL | ARF1 | BASP1 | CACNG1 | CCR3 | CD47 | CDIPT | CLDN7 | CRYAB | DDR1 | EBI3 | EPB41L1 | FAP |
| ADAM23 | ALPP | ARF4 | BBS1 | CACNG2 | CCR3 | CD47 | CDK14 | CLDN8 | CRYAB | DDR2 | EBP | EPB41L1 | FAS |
| ADAM28 | ALPPL2 | ARF5 | BBS2 | CACNG3 | CCR4 | CD48 | CDK5R1 | CLEC10A | CRYAB | DEF6 | ECE1 | EPB41L5 | FASLG |
| ADAP1 | AMBp | ARF6 | BBS4 | CACNG4 | CCR5 | CD5 | CDSN | CLEC1A | CSDA | DEGS1 | ECEL1 | EPCAM | FBLIM1 |
| ADAP2 | AMICA1 | ARFGAP2 | BBS5 | CACNG6 | CCR6 | CD52 | CEACAM1 | CLEC1B | CSF1 | DES | ECSLR | EPHA10 | FCAMR |
| ADCY5 | AMIGO2 | ARFIP2 | BBS7 | CACNG7 | CCR6 | CD53 | CEACAM5 | CLEC2B | CSF1R | DGKA | EDA | EPHA2 | FCAR |
| ADCY8 | AMOT | ARHGAP17 | BCAP31 | CADM3 | CCR6 | CD55 | CEACAM6 | CLEC2D | CSF2RA | DGKK | ECA2R | EPHA3 | FCER1A |
| ADCYAP1R1 | AMOTL1 | ARHGEF1 | BCL10 | CALCR | CCR7 | CD58 | CEACAM8 | CLEC4A | CSF2RB | DGKQ | EDG1 | EPHA4 | FCER1G |
| ADD1 | AMPH | ARHGEF1 | BCL2 | CALCR | CCR7 | CD59 | CERCAM | CLEC4M | CSF3R | DGKZ | EDG2 | EPHA6 | FCER2 |
| ADD2 | AMTN | ARHGEF2 | BDKRB1 | CALCRL | CCR7 | CD6 | CFB | CLEC5A | CSK | DHH | EDG3 | EPHA7 | FCGR1A |
| ADI1 | ANGPT1 | ARHGEF2 | BDKRB1 | CALCRL | CCR7 | CD63 | CFC1 | CLEC7A | CSNK2A1 | DI03 | EDG3 | EPHA8 | FCGR1B |
| ADIPOR1 | ANGPT1 | ARHGEF4 | BDKRB2 | CALCRL | CCR8 | CD68 | CHIC2 | CLIC1 | CSNK2B | DIRAS1 | EDG4 | EPHB1 | FCGR2A |
| ADORA1 | ANGPT2 | ARRB1 | BDKRB2 | CALHM1 | CCR8 | CD69 | CHRFAM7A | CLIC4 | CSPG5 | DIRAS2 | EDG4 | EPHB2 | FCGR2B |
| ADORA1 | ANKH | ARRB2 | BDKRB2 | CALM3 | CCR8 | CD7 | CHRM1 | CLPTM1 | CTGF | DIRAS3 | EDG5 | EPHB3 | FCGR3A |
| ADORA1 | ANKRD20A1 | ARSA | BEST1 | CALN1 | CCR9 | CD7 | CHRM1 | CLSTN1 | CTNNNA1 | DKK1 | EDG6 | EPHB4 | FCGR3B |
| ADORA1 | ANKS1B | ARSA | BEST3 | CALR | CCRL1 | CD70 | CHRM1 | CLSTN2 | CTNNNA2 | DLG2 | EDG6 | EPHB6 | FCGRT |
| ADORA2A | ANKS4B | ARSA | BFAR | CAMK1G | CCRL2 | CD73 | CHRM2 | CMKLRI | CTSB | DLG4 | EDG7 | EPOR | FCRL1 |
| ADORA2A | ANO2 | ART3 | BGN | CAMK2A | CCRL2 | CD74 | CHRM2 | CNKSRI | CTSG | DLGAP1 | EDG8 | ERAS | FCRL3 |
| ADORA2B | ANO2 | ASAM | BLR1 | CAMK2B | CCRL2 | CD79A | CHRM2 | CNKSRI | CTSG | DLGAP1 | EDG8 | ERAS | FCRL3 |
| ADORA2B | ANTXR1 | ASAP2 | BMF | CAMK2B | CD109 | CD79B | CHRM3 | CNNM1 | CTSL2 | DLK1 | EDNRA | ERBB2 | FCRL4 |
| ADORA3 | ANTXR2 | ASGR1 | BMPR1A | CAMK2D | CD109 | CD80 | CHRM3 | CNNM3 | CX3CL1 | DLL1 | EDNRA | ERBB2 | FCRL5 |
| ADORA3 | ANXA1 | ATF4 | BMPR1B | CAMK2G | CD14 | CD82 | CHRM3 | CNNM4 | CX3CL1 | DLL1 | EDNRB | ERBB3 | FERMT1 |
| ADRA1A | ANXA13 | ATF4 | BMPR2 | CAMK2N1 | CD14 | CD83 | CHRM4 | CNPY2 | CX3CR1 | DLST | EFNA1 | ERBB4 | FERMT2 |
| ADRA1B | ANXA2 | ATP12A | BPI | CAMKV | CD151 | CD84 | CHRM4 | CNR1 | CX3CR1 | DNAJB4 | EFNA2 | EREG | FEZ1 |
| ADRA1D | ANXA3 | ATP1A2 | BRAF | CAP1 | CD160 | CD86 | CHRM4 | CNR1 | CX3CR1 | DNAL4 | EFNA2 | ERMAP | FFAR1 |
| ADRA1D | ANXA6 | ATP1A3 | BRS3 | CAP2 | CD163 | CD8A | CHRM5 | CNR2 | CX3CR1 | DNMBP | EFNA3 | ERMN | FFAR2 |
| ADRA2A | ANXA7 | ATP1B1 | BRS3 | CAPN1 | CD164 | CD8B | CHRM5 | CNR2 | CXADR | DOC2B | EFNA4 | ERRFI1 | FFAR2 |
| ADRA2A | AOC2 | ATP1B2 | BSG | CAPN10 | CD177 | CD9 | CHRM5 | CNR2 | CXCL16 | DOC2B | EFNB1 | ERVFRDE1 | FFAR3 |
| ADRA2B | AOC3 | ATP1B3 | BSND | CAPN2 | CD19 | CD93 | CHRNA10 | CNST | CXCR1 | DPEP1 | EFNB2 | ESAM | FFAR3 |
| ADRA2C | AP1S1 | ATP2A2 | BST1 | CAPN2 | CD1A | CD93 | CHRNA10 | CNST | CXCR1 | DPEP1 | EFNB3 | ESR1 | FGA |

| | | | | | | | | | | | | | |
|---------|---------|---------|---------|---------|--------|----------|----------|---------|----------|----------|---------|----------|---------|
| FGB | GABRA4 | GJD3 | GPR113 | GPR3 | GPRC5A | HLA-C | IFNAR1 | JAG1 | KCTD7 | LPAR6 | MCC | MTDH | NPY2R |
| FGD2 | GABRA5 | GJD4 | GPR113 | GPR31 | GPRC5A | HLA-DMA | IFNAR2 | JAM2 | KCTD9 | LPHN1 | MCF2L | MTNR1A | NPY2R |
| FGF10 | GABRA6 | GLP1R | GPR114 | GPR31 | GPRC5B | HLA-DMB | IFNGR1 | JAM3 | KCTD9 | LPL | MCHR1 | MTNR1B | NPY5R |
| FGF6 | GABRB1 | GLP2R | GPR115 | GPR32 | GPRC5B | HLA-DOA | IFNGR2 | JPH3 | KDR | LRFN3 | MCHR1 | MTNR1B | NRCAM |
| FGFBP1 | GABRB1 | GLP2R | GPR116 | GPR34 | GPRC5B | HLA-DOB | IGDCC4 | JUB | KEL | LRP1 | MCHR2 | MUC1 | NRG1 |
| FGFR1 | GABRB3 | GLRA2 | GPR116 | GPR35 | GPRC5C | HLA-DPA1 | IGF1R | JUP | KGP | LRP10 | MDGA1 | MUC15 | NRG1 |
| FGFR2 | GABRD | GLRA3 | GPR119 | GPR35 | GPRC5C | HLA-DPB1 | IGHG3 | KARS | KIAA1919 | LRP12 | MDGA1 | MUC20 | NRG2 |
| FGFR3 | GABRE | GLRB | GPR12 | GPR35 | GPRC5C | HLA-DQA1 | IGSF11 | KBTBD10 | KIFC3 | LRP3 | MDGA1 | MUC21 | NRG3 |
| FGFR4 | GABRG1 | GM2A | GPR12 | GPR35 | GPRC5D | HLA-DQB1 | IGSF5 | KCNA1 | KIR2DL1 | LRP8 | MDGA2 | MUC4 | NRG4 |
| FGFRL1 | GABRQ | GNA13 | GPR125 | GPR37 | GPRC6A | HLA-DRA | IGSF6 | KCNA2 | KIR2DL2 | LRPAP1 | MDM2 | MUSK | NRPI |
| FGG | GAD2 | GNA14 | GPR128 | GPR37L1 | GPRC6A | HLA-DRB1 | IGSF9 | KCNA3 | KIR2DL3 | LRRC32 | MEGF10 | MYH9 | NRP2 |
| FHIT | GAK | GNA14 | GPR132 | GPR39 | GPSM1 | HLA-DRB3 | IL10RA | KCNA4 | KIR2DL4 | LSAMP | MEGF11 | MYH9 | NRSN2 |
| FLNB | GAL3ST1 | GNAI1 | GPR132 | GPR4 | GRB10 | HLA-DRB4 | IL10RB | KCNA6 | KIR2DL5A | LSR | MET | NAALADL1 | NTNG1 |
| FLOT1 | GALR1 | GNAI1 | GPR132 | GPR4 | GRIA4 | HLA-DRB5 | IL11RA | KCNB1 | KIR2DL5B | LTB4R | MFAP3 | NAB1 | NTRK2 |
| FLOT2 | GALR1 | GNAI2 | GPR133 | GPR40 | GRID1 | HLA-E | IL12RB1 | KCND1 | KIR2DS1 | LTB4R | MFGE8 | NAE1 | NTRK3 |
| FLRT1 | GALR2 | GNAI3 | GPR135 | GPR42 | GRIK1 | HMOX2 | IL12RB2 | KCNE1L | KIR2DS3 | LTB4R2 | MF2 | NCAM1 | NTSR1 |
| FLRT3 | GALR3 | GNAO1 | GPR135 | GPR44 | GRIK3 | HMOX2 | IL13RA1 | KCNE2 | KIR2DS3 | LTB4R2 | MGST2 | NCAM2 | NTSR1 |
| FLT1 | GAP43 | GNAQ | GPR137B | GPR45 | GRIK3 | HOMER1 | IL17RA | KCNE4 | KIR2DS5 | LY6D | MICA | NCKAP1 | NTSR1 |
| FLT3LG | GAP43 | GNAQ | GPR139 | GPR5 | GRIK5 | HOMER2 | IL17RB | KCNG1 | KIR3DL1 | LY6E | MICB | NCR1 | NTSR2 |
| FLT4 | GAP43 | GNAQ | GPR141 | GPR50 | GRIN2C | HOMER3 | IL18R1 | KCNG3 | KIR3DS1 | LY6G6C | MLANA | NCR2 | NTSR2 |
| FLVCR1 | GBA2 | GNAS | GPR142 | GPR52 | GRIN3A | HPN | IL1R1 | KCNG4 | KIRREL3 | LY6G6D | MLNR | NCR3 | OCLN |
| FLVCR2 | GBAS | GNAS | GPR142 | GPR53 | GRK5 | HRH1 | IL1RAP | KCNH2 | KISS1R | LY6G6F | MLNR | NDRG1 | OLR1 |
| FMN1 | GBP1 | GNAT2 | GPR142 | GPR55 | GRK6 | HRH1 | IL1RAPL1 | KCNH6 | KLHL17 | LY6H | MMD | NECAP2 | OMG |
| FOLH1 | GBP2 | GNAZ | GPR143 | GPR55 | GRM1 | HRH2 | IL1RL1 | KCNIP2 | KLRC1 | LY6K | MME | NEDD4 | OPALIN |
| FOLR1 | GBP5 | GNAZ | GPR146 | GPR56 | GRM2 | HRH2 | IL23R | KCNIP3 | KLRC2 | LY86 | MMGT1 | NETO1 | OPALIN |
| FOLR2 | GCA | GNB2L1 | GPR146 | GPR6 | GRM3 | HRH3 | IL28RA | KCNJ10 | KLRD1 | LY96 | MMPI4 | NEU1 | OPNLW |
| FOLR2 | GCGR | GNB2L1 | GPR149 | GPR6 | GRM3 | HRH3 | IL2RA | KCNJ11 | KLRF1 | LYPD1 | MMPI6 | NEU1 | OPN1MW |
| FOLR2 | GDPD2 | GNB5 | GPR149 | GPR61 | GRM7 | HRH4 | IL2RA | KCNJ11 | KLRK1 | LYPD2 | MMP2 | NF2 | OPNSW |
| FPR1 | GEM | GNG11 | GPR15 | GPR62 | GRM8 | HRH4 | IL2RB | KCNJ12 | KRAS | LYPD3 | MMP25 | NF2 | OPN4 |
| FPR2 | GFRA1 | GNG3 | GPR150 | GPR62 | GRPR | HSD17B7 | IL2RG | KCNJ14 | LAG3 | LYPD4 | MOG | NFAM1 | OPN5 |
| FPR3 | GFRA3 | GNGT1 | GPR150 | GPR63 | GRPR | HSD17B8 | IL31RA | KCNJ2 | LAIR1 | LYPD5 | MPL | NFIA | OPRD1 |
| FPRL1 | GGT5 | GNRH1 | GPR151 | GPR63 | GSR | HSPB1 | IL4R | KCNJ3 | LAMP1 | LYPD6B | MPL | NGEF | OPRD1 |
| FPRL2 | GHRHR | GNRHR | GPR151 | GPR64 | GUCA1B | HSPB1 | IL6R | KCNJ6 | LAMP2 | LYVE1 | MPP5 | NGFR | OPRK1 |
| FRK | GHRHR | GOT2 | GPR152 | GPR65 | GUCY2D | HTR1A | IL6ST | KCNJ8 | LASP1 | M6PR | MPP5 | NIPA1 | OPRK1 |
| FRS2 | GHSR | GP1BA | GPR156 | GPR65 | GUCY2F | HTR1B | IL7R | KCNK5 | LAT | MAGEA1 | MRI | NIPA1 | OPRL1 |
| FRS3 | GHSR | GP1BB | GPR157 | GPR68 | GYP4 | HTR1D | IL9R | KCNK6 | LAT2 | MAGED1 | MRI | NKAIN3 | OPRL1 |
| FSHR | GIF | GP2 | GPR157 | GPR75 | GYPB | HTR1E | ILDR1 | KCNK9 | LAX1 | MAGEE1 | MRAP | NKG7 | OPRL1 |
| FSHR | GIPR | GP5 | GPR160 | GPR77 | GYPD | HTR1E | ILK | KCNMB1 | LCK | MAGI11 | MRAS | NLGN1 | OPRL1 |
| FSHR | GIPR | GP9 | GPR161 | GPR77 | GYPE | HTR1F | INSRR | KCNMB2 | LCPI | MAL2 | MRG | NMBR | OPRM1 |
| FSHR | GIPR | GPA33 | GPR162 | GPR77 | GZMA | HTR2A | IRS1 | KCNMB4 | LEPR | MALL | MRGPRD | NMBR | OR10G3 |
| FURIN | GIT1 | GPBAR1 | GPR17 | GPR78 | GZMB | HTR2B | IRS4 | KCNN3 | LEPROT | MAP7 | MRGPRD | NMBR | OR10T2 |
| FUT1 | GIT2 | GPC2 | GPR17 | GPR81 | HAS3 | HTR2B | ITGA1 | KCNN4 | LGALS3 | MAPKAP1 | MRGPRD | NMBR | OR11G2 |
| FXYD1 | GIT2 | GPC2 | GPR171 | GPR81 | HBEGF | HTR2C | ITGA10 | KCNRG | LGR4 | MARCKSL1 | MRGPRF | NMBR | OR13C4 |
| FXYD2 | GIT3 | GPC3 | GPR171 | GPR81 | HCK | HTR3A | ITGA2 | KCN51 | LGR5 | MARCKSL1 | MRGPRX1 | NMBR | OR13C4 |
| FXYD3 | GJA1 | GPC4 | GPR173 | GPR82 | HCN2 | HTR3B | ITGA4 | KCN52 | LGR6 | MARCO | MRGPRX1 | NMUR1 | OR13C8 |
| FXYD6 | GJA10 | GPC5 | GPR173 | GPR83 | HCRT | HTR4 | ITGA4 | KCN53 | LHCGR | MARK2 | MRGPRX1 | NMUR1 | OR13C8 |
| FXYD6 | GJA10 | GPER | GPR173 | GPR84 | HCRT1 | HTR5A | ITGA5 | KCN53 | LIFR | MARVELD2 | MRGPRX1 | NMUR2 | OR13C9 |
| FYN | GJA4 | GPER | GPR176 | GPR84 | HCRT2 | HTR6 | ITGA6 | KCN52 | LIFR | MAS1 | MRGPRX2 | NOD2 | OR13C9 |
| FZD10 | GJA5 | GPHN | GPR18 | GPR85 | HCRT2 | HTR7 | ITGA8 | KCNV1 | LILRA3 | MAS1L | MRGPRX2 | NOD2 | OR14A16 |
| FZD4 | GJA8 | GPIHBP1 | GPR182 | GPR85 | HDAC11 | HTR7 | ITGB1 | KCTD10 | LILRB1 | MC1R | MRGPRX4 | NOSTRIN | OR14A16 |
| FZD5 | GJA8 | GPNMB | GPR182 | GPR85 | HDAC11 | HYAL2 | ITGB1 | KCTD12 | LILRB2 | MC1R | MRGPRX4 | NPBWR1 | OR1D5 |
| FZD7 | GJA9 | GPR | GPR183 | GPR85 | HDAC6 | ICAM1 | ITGB2 | KCTD13 | LILRB4 | MC1R | MRGPRX4 | NPBWR2 | OR1E1 |
| FZD9 | GJB1 | GPR | GPR20 | GPR85 | HDLBP | ICAM2 | ITGB2 | KCTD14 | LIME1 | MC2R | MRGPRX4 | NPFFR1 | OR1G1 |
| G3BP1 | GJB2 | GPR1 | GPR21 | GPR85 | HFE | ICAM3 | ITGB5 | KCTD15 | LMBR1L | MC3R | MRGPRX4 | NPFFR2 | OR1J2 |
| GAB2 | GJB4 | GPR101 | GPR22 | GPR87 | HHIP | ICAM4 | ITGB6 | KCTD16 | LNPEP | MC4R | MRGXP1 | NPHS1 | OR1J2 |
| GABARAP | GJB5 | GPR103 | GPR23 | GPR88 | HIP1R | ICOS | ITGB7 | KCTD17 | LPAR1 | MC4R | MS4A1 | NPR2 | OR1J4 |
| GABBR2 | GJB7 | GPR109A | GPR25 | GPR89 | HIP1R | IFITM1 | ITGB8 | KCTD18 | LPAR2 | MC5R | MS4A2 | NPTXR | OR1L1 |
| GABRA1 | GJC3 | GPR109B | GPR26 | GPR92 | HLA-A | IFITM3 | ITGBL1 | KCTD4 | LPAR3 | MCSR | MSLN | NPTXR | OR1L1 |
| GABRA2 | GJC3 | GPR110 | GPR27 | GPR97 | HLA-A | IFITM3 | ITLN1 | KCTD5 | LPAR4 | MCAM | MSN | NPY1R | OR1N1 |
| GABRA3 | GJD3 | GPR111 | GPR27 | GPR98 | HLA-B | IFITM3 | ITM2B | KCTD6 | LPAR5 | MCC | MST1R | NPY1R | OR1N1 |

| | | | | | | | | | | | | | |
|--------|---------|----------|---------|---------|---------|----------|----------|----------|----------|---------|---------|------------|---------|
| OR2C3 | OR9G1 | PCDHB2 | PLAUR | PTPN4 | RAMP1 | RXFP2 | SILV | SLC23A2 | SLC4A4 | SSTR1 | TAF12 | TMEM123 | TSPAN13 |
| OR2M4 | OR9G1 | PCDHB5 | PLCG2 | PTPRA | RAMP1 | RXFP2 | SIRPA | SLC24A6 | SLC4A7 | SSTR1 | TAGLN2 | TMEM150A | TSPAN15 |
| OR2M4 | OSCAR | PCDHB5 | PLD2 | PTPRC | RAMP2 | RXFP3 | SIRPB1 | SLC25A11 | SLC5A1 | SSTR2 | TAOK3 | TMEM173 | TSPAN31 |
| OR2T1 | OSCP1 | PCDHB6 | PLD2 | PTPRCAP | RAMP3 | RXFP3 | SKAP2 | SLC25A13 | SLC5A1 | SSTR3 | TAPBPL | TMEM204 | TSPAN4 |
| OR2T35 | OSMR | PCDHB6 | PLEK2 | PTPRD | RAPIA | RXFP4 | SLAMF1 | SLC25A14 | SLC5A1 | SSTR3 | TAS1R2 | TMEM25 | TSPAN7 |
| OR3A2 | OXER1 | PCDHB7 | PLEKHA1 | PTPRE | RAPIB | RYK | SLAMF7 | SLC25A17 | SLC5A1 | SSTR4 | TAS1R3 | TMEM47 | TSPAN9 |
| OR3A2 | OXGR1 | PCDHGA10 | PLEKHA2 | PTPRG | RAP2A | RYK | SLAMF7 | SLC25A3 | SLC5A12 | SSTR5 | TAS2R1 | TMEM50B | TST |
| OR4C45 | OXGR2 | PCDHGA11 | PLEKH01 | PTPRJ | RAP2B | S100A12 | SLAMF7 | SLC25A4 | SLC5A3 | SSTR5 | TAS2R10 | TMEM8A | TYRO3 |
| OR4C45 | OXTR | PCDHGA12 | PLEKH01 | PTPRM | RAP2C | S100A6 | SLC10A1 | SLC25A5 | SLC5A3 | SSTR5 | TAS2R13 | TMEM90B | TYROBP |
| OR4D2 | P2RX1 | PCDHGA2 | PLIN2 | PTPRN | RAP2C | S100A7 | SLC10A6 | SLC26A2 | SLC5A6 | ST14 | TAS2R14 | TMEM97 | UBAC1 |
| OR4D2 | P2RX4 | PCDHGA3 | PLSCR1 | PTPRN2 | RAPGEF4 | S100A8 | SLC11A1 | SLC26A5 | SLC5A7 | STAT3 | TAS2R14 | TMPPRSS11B | UBE2B |
| OR4E2 | P2RX5 | PCDHGA4 | PLSCR3 | PTPRO | RAPGEF4 | S100A9 | SLC11A2 | SLC26A8 | SLC6A1 | STAT3 | TAS2R16 | TMPPRSS11D | UBL3 |
| OR4E2 | P2RX7 | PCDHGA4 | PLXNC1 | PTPRR | RAPH1 | S100G | SLC12A1 | SLC27A1 | SLC6A11 | STEAP1 | TAS2R16 | TMPPRSS11E | UBL3 |
| OR4N2 | P2RY1 | PCDHGA5 | PMEPA1 | PTPRS | RASD1 | S1PRI | SLC12A3 | SLC27A6 | SLC6A13 | STEAP2 | TAS2R3 | TMPPRSS2 | UCHL1 |
| OR4N2 | P2RY1 | PCDHGA8 | POTED | PTPRT | RASD2 | S1PRI3 | SLC12A4 | SLC28A2 | SLC6A15 | STEAP2 | TAS2R39 | TMPPRSS5 | UMODL1 |
| OR4Q3 | P2RY10 | PCDHGB1 | PPAP2B | PTPRU | RASD2 | S1PRI4 | SLC12A6 | SLC29A1 | SLC6A16 | STEAP3 | TAS2R39 | TMPPRSS6 | UNC5A |
| OR4Q3 | P2RY10 | PCDHGB2 | PPYR1 | PVR | RASGRP1 | S1PRI5 | SLC12A7 | SLC2A13 | SLC6A17 | STEAP4 | TAS2R43 | TMPPRSS9 | UPK1A |
| OR4S2 | P2RY11 | PCDHGB6 | PRAME | PVRL1 | RASL10A | S1PRI5 | SLC12A9 | SLC2A2 | SLC6A18 | STIM1 | TAS2R5 | TNF | UPK3A |
| OR51A2 | P2RY12 | PCDHGB6 | PRAME | PVRL2 | RECK | SC4MOL | SLC13A1 | SLC2A4 | SLC6A19 | STOM | TAS2R5 | TNFAPI1 | UPK3B |
| OR51B6 | P2RY12 | PCDHGC3 | PRGER1 | PVRL3 | RELT | SCAMP5 | SLC13A1 | SLC2A5 | SLC6A3 | STOML3 | TAS2R5 | TNFRSF10B | USP14 |
| OR51B6 | P2RY13 | PCDHGC4 | PRKCA | PVRL4 | RGMA | SCAR5 | SLC13A2 | SLC2A6 | SLC6A4 | STX1A | TAS2R7 | TNFRSF10C | VAMP5 |
| OR51E1 | P2RY14 | PCDHGC5 | PRKCB | QKI | RGNEF | SCARB1 | SLC13A3 | SLC2A8 | SLC6A5 | STX1B | TAS2R7 | TNFRSF12A | Vav2 |
| OR51E2 | P2RY14 | PCYOX1 | PRKCH | RAB10 | RGR | SCARB2 | SLC14A1 | SLC2A9 | SLC6A6 | STX2 | TAS2R8 | TNFRSF13C | Vav2 |
| OR51E2 | P2RY2 | PDCD1 | PRKCZ | RAB11A | RGS1 | SCN2B | SLC15A1 | SLC30A10 | SLC6A7 | STX3 | TAS2R8 | TNFRSF14 | VAV3 |
| OR51E2 | P2RY2 | PDCD10 | PRKD1 | RAB13 | RGS13 | SCN3B | SLC15A2 | SLC30A5 | SLC6A8 | STX4 | TAS2R9 | TNFRSF17 | VCAM1 |
| OR51L1 | P2RY4 | PDE4A | PRLHR | RAB13 | RGS13 | SCNN1A | SLC16A1 | SLC30A8 | SLC7A1 | STX6 | TBXA2R | TNFRSF18 | VDAC1 |
| OR51L1 | P2RY5 | PDE6C | PRLHR | RAB13 | RGS13 | SCNN1B | SLC16A1 | SLC30A8 | SLC7A10 | STX8 | TBXA2R | TNFRSF1A | VIP |
| OR51V1 | P2RY5 | PDE9A | PRMT8 | RAB13 | RGS7 | SCNN1G | SLC16A10 | SLC31A1 | SLC7A11 | STXBPI | TICRG1 | TNFRSF1B | VIPR1 |
| OR52A1 | P2RY6 | PDGFRA | PRNP | RAB14 | RHAG | SCRIB | SLC16A14 | SLC31A2 | SLC7A2 | STXBPSL | TDGF1 | TNFRSF25 | VIPR2 |
| OR52A5 | P2RY6 | PDGFRB | PROC | RAB14 | RHO | SCTR | SLC16A4 | SLC33A1 | SLC7A3 | STYK1 | TEK | TNFRSF9 | VIPR2 |
| OR52A5 | P2RY6 | PDI46 | PROCR | RAB17 | RHO | SCTR | SLC16A5 | SLC34A1 | SLC7A5 | SUCNR1 | TFRC | TNFSF11 | VIPR2 |
| OR52II | P2RY8 | PDLIM5 | PROKR2 | RAB18 | RHO | SCUBE1 | SLC16A7 | SLC35A1 | SLC7A6 | SUCNR1 | TGFA | TNFSF12 | VN1R1 |
| OR52II | PACSI3N | PDLIM5 | PROM1 | RAB23 | RHOA | SDC1 | SLC16A8 | SLC36A1 | SLC7A7 | SV2B | TGFBR1 | TNFSF13B | VN1R1 |
| OR52M1 | PAG1 | PDLIM5 | PROM1 | RAB25 | RHOB | SDC2 | SLC17A3 | SLC36A1 | SLC7A8 | SV2C | TGFBR2 | TNFSF14 | VN1R5 |
| OR5AC2 | PAK1 | PDLIM5 | PROM2 | RAB2B | RHOC | SDC4 | SLC17A4 | SLC36A2 | SLC7A9 | SYMPK | TGFBR3 | TNFSF15 | VSIG2 |
| OR5AC2 | PANX2 | PDLIM5 | PRR7 | RAB30 | RHOD | SDCBP | SLC17A5 | SLC38A1 | SLC9A3R1 | SYNGR2 | TGOLN2 | TNFSF4 | VTCN1 |
| OR5D14 | PANX3 | PDLIM5 | PRSS8 | RAB31 | RHOH | SECTM1 | SLC17A7 | SLC38A2 | SLC9A4 | SYNPO | THBD | TNFSF8 | WWP1 |
| OR5D14 | PAQR7 | PDLIM5 | PSCA | RAB35 | RIN1 | SELL | SLC18A2 | SLC38A3 | SLC9A6 | SYT8 | THBS1 | TNK2 | XCR1 |
| OR5D16 | PAQR8 | PDPK1 | PSD3 | RAB35 | RNPEP | SELP | SLC18A3 | SLC38A3 | SLCO1A2 | SYTL1 | THY1 | TP53I13 | XCR1 |
| OR5D16 | PARD6A | PDPK1 | PSD3 | RAB38 | ROBO2 | SELPLG | SLC19A1 | SLC38A4 | SLCO1B3 | TAARI | THY1 | TRAF6 | YIPF3 |
| OR5H1 | PARMI | PDPN | PSEN2 | RAB39B | ROR1 | SEMA4A | SLC19A2 | SLC38A5 | SLCO2A1 | TAAR2 | THY1 | TRAK2 | YIPF3 |
| OR5J2 | PARMI | PECAM1 | PSENEN | RAB3A | RPSA | SEMA4F | SLC1A1 | SLC38A5 | SLCO4C1 | TAAR2 | TICAM2 | TRAT1 | ZBTB33 |
| OR5K1 | PARVG | PERP | PTAFR | RAB4A | RRAD | SEMA6D | SLC1A2 | SLC39A1 | SLCO4C1 | TAAR3 | TIE1 | TRDN | ZP3 |
| OR5K1 | PCDH10 | PHKA2 | PTAFR | RAB4A | RRAS | SEPT2 | SLC1A3 | SLC39A4 | SNAP25 | TAAR3 | TIGIT | TREM1 | ZP3 |
| OR5M9 | PCDH11X | PHKB | PTAFR | RAB4A | RRH | SEPT5 | SLC1A4 | SLC39A5 | SNAP25 | TAAR5 | TIRAP | TREM2 | ZYX |
| OR5M9 | PCDH11Y | PICK1 | PTAFR | RAB4B | RSC1A1 | SEPT11 | SLC1A5 | SLC39A6 | SNAP29 | TAAR5 | TJP1 | TRHR | |
| OR5P3 | PCDH17 | PICK1 | PTCH1 | RAB5A | RTKN2 | SERBP1 | SLC1A6 | SLC3A1 | SNCA | TAAR5 | TJP2 | TRIP10 | |
| OR5V1 | PCDH18 | PIGU | PTGDR | RAB5A | RTN4 | SERBP1 | SLC20A1 | SLC3A2 | SNOR25 | TAAR6 | TJP2 | TRO | |
| OR6C2 | PCDHA1 | PIK3AP1 | PTGER1 | RAB5A | RTN4 | SERBP1 | SLC20A2 | SLC40A1 | SNOR25 | TAAR8 | TJP2 | TRPC5 | |
| OR6C3 | PCDHA10 | PIK3AP1 | PTGER2 | RAB5B | RTN4 | SERINC3 | SLC22A11 | SLC41A1 | SNOR25 | TAAR8 | TLR1 | TRPM8 | |
| OR6C3 | PCDHA2 | PILRA | PTGER3 | RAB5C | RTN4 | SERPINE1 | SLC22A12 | SLC41A2 | SNX20 | TAAR9 | TLR2 | TRPV1 | |
| OR7C2 | PCDHA4 | PILRB | PTGER4 | RAB7L1 | RTN4 | SEZ6 | SLC22A13 | SLC41A3 | SNX9 | TAAR9 | TLR3 | TRPV2 | |
| OR7C2 | PCDHA6 | PIP5K1C | PTGFR | RAB8A | RTN4 | SGCD | SLC22A18 | SLC43A1 | SOCS7 | TAAR9 | TLR7 | TRPV4 | |
| OR7D2 | PCDHA7 | PKD2 | PTGIR | RAB9A | RTN4R | SH3KBP1 | SLC22A2 | SLC43A2 | SORBS1 | TAC1 | TLR9 | TRPV5 | |
| OR7E24 | PCDHA8 | PKD2L1 | PTGS1 | RABAC1 | RTN4R | SHANK2 | SLC22A4 | SLC44A1 | SORBS1 | TACR1 | TM4SF1 | TRPV6 | |
| OR7E24 | PCDHAC2 | PKN1 | PTHR1 | RABEPK | RTP1 | SHH | SLC22A5 | SLC46A1 | SPAM1 | TACR1 | TM9SF2 | TSG101 | |
| OR8G1 | PCDHB12 | PKR1 | PTK7 | RAC1 | RTP2 | SIGLEC10 | SLC22A6 | SLC46A2 | SPN | TACR2 | TMBIM6 | TSHR | |
| OR8G1 | PCDHB13 | PLA2G16 | PTP4A1 | RAC1 | RXFP1 | SIGLEC6 | SLC22A7 | SLC47A1 | SPRY2 | TACR2 | TMED1 | TSHR | |
| OR8U8 | PCDHB15 | PLA2G3 | PTP4A1 | RAET1L | RXFP1 | SIGLEC7 | SLC22A8 | SLC4A1 | SPRY2 | TACR3 | TMEFF1 | TSHR | |
| OR8U8 | PCDHB16 | PLA2R1 | PTP4A2 | RAET1L | RXFP2 | SIGMAR1 | SLC23A1 | SLC4A2 | SRC | TACSTD2 | TMEM11 | TSPAN12 | |

Table S2. Recombinant proteins used in the study: annotation, primers (published in³⁰) and production method

| Recombinant Protein, in insect cells | Gene | Group | DC | gDNA origin | Forward cloning primer | Reverse cloning primer | | | |
|--|------------------|------------------|-------|-----------------|---|--|--|--|-------------------|
| FULL LENGTH | <i>IT4var20</i> | B/A | DC8 | FCR3/IT | Codon optimized sequence encoding from start Met to Cys2508 | | | | |
| FULL LENGTH | <i>IT4var13</i> | B | DC17 | FCR3/IT | Codon optimized sequence encoding from start Met to Cys2691 | | | | |
| CIDRa1.1 | <i>IT4var20</i> | B/A | DC8 | FCR3/IT | Published in (31) | | | | |
| CIDRa1.1 | <i>PFD0020c</i> | A | DC8 | FCR3/IT | Published in (31) | | | | |
| DBLα2 | CIDRa1.1 DBLβ12 | <i>IT4var06</i> | B/A | DC8 | FCR3/IT | TGCCCACTTAATTATAAAATTC CCATATGATTATGATGATGCATTACGTTGT | | | |
| CIDRa1.4 | <i>HB3var03</i> | A | DC13 | HB3 | | Published in (31) | | | |
| DBLα1.7 | CIDRa1.4 DBLβ1 | <i>DD2var32</i> | A | DC13 | DD2 | ATGGGGGGAAATTCTCAAAGGTGCTCCT CCACCTGATTGAAAAAGCTTGGCAATGT | | | |
| DBLα1.7 | CIDRa1.4 DBLβ3 | <i>PF11_0521</i> | A | DC13 | 3D7 | ATGGGGAATGCAAATCCAGCGACTCCGGAT GCATTTACATGCTGTATCATGATCATGTGG | | | |
| DBLα1.4 | CIDRa1.7 DBLβ3 | <i>IT4var22</i> | A | no DC | FCR3/IT | ATGGGGTCAAAATCATCAAAACCTTCGAAA CCTTATGACCATGCAAAGCATGTAAATTGT | | | |
| DBLα1.2 | CIDRa1.5 | <i>DD2var43</i> | A | DC15 | DD2 | ATGGCACCAAGCGTAGACGTATAATGAA ACATGGTTGGATGGAATTATTCAGGCA | | | |
| CIDRa1.6 | <i>PFD1235w</i> | A | DC4 | 3D7 | | Published in (31) | | | |
| CIDRa1.6 | <i>IT4var18</i> | A | no DC | FCR3/IT | | Published in (31) | | | |
| CIDRa1.6 | <i>HB3var02</i> | A | DC4 | HB3 | | Published in (31) | | | |
| CIDRa1.6 | <i>PF08_0140</i> | B/A | DC8 | 3D7 | | Published in (31) | | | |
| CIDRa1.3 | <i>PFE1640w</i> | A | DC1 | 3D7 | | Published in (31) | | | |
| CIDRa2.8 | <i>MCvar01</i> | B | no DC | MC | | Published in (31) | | | |
| CIDRδ1 | <i>HB3var05</i> | A | DC16 | HB3 | | Published in (31) | | | |
| CIDRδ2 | <i>HB3var01</i> | A | DC16 | HB3 | | Published in (31) | | | |
| CIDRδ1 | <i>HB3var06</i> | A | DC16 | HB3 | | Published in (31) | | | |
| CIDRa5 | <i>IT4var14</i> | B | DC17 | FCR3/IT | | Published in (31) | | | |
| CIDRa3.1 | <i>HB3var27</i> | B | no DC | HB3 | | Published in (31) | | | |
| CIDRa3.2 | <i>HB3var13</i> | B | no DC | HB3 | | Published in (31) | | | |
| CIDRa2.10 | <i>PFD0005w</i> | B | no DC | 3D7 | | Published in (31) | | | |
| CIDRa2.11 | <i>PF08_0142</i> | B | no DC | 3D7 | | Published in (31) | | | |
| CIDRa3.5 | <i>IT4var15</i> | B | no DC | FCR3/IT | | Published in (31) | | | |
| CIDRa2.2 | <i>PF08_0103</i> | B | no DC | 3D7 | | Published in (31) | | | |
| CIDRa3.1 | <i>DD2var01</i> | B | DC14 | DD2 | | Published in (31) | | | |
| FULL LENGTH | <i>PFI1820w</i> | A | DC3 | 3D7 | | Published in (31) | | | |
| FULL LENGTH | <i>PFL0030c</i> | E | DC2 | FCR3/IT | Codon optimized sequence encoding from start Met to Phe2649 | | | | |
| DBLβ12 | <i>PFD0020c</i> | A | DC8 | 3D7 | | Published in (31) | | | |
| DBLy6 | <i>PFD0020c</i> | A | DC8 | 3D7 | | Published in (31) | | | |
| DBLβ12 | DBLy6 | <i>PFD0020c</i> | A | DC8 | 3D7 | Published in (31) | | | |
| DBLα2 | <i>IT4var20</i> | B/A | DC8 | FCR3/IT | | Published in (31) | | | |
| DBLβ12 | <i>IT4var20</i> | B/A | DC8 | FCR3/IT | AACCCCTGTGGAAAAAACCC | ACATTTACACGCCCTTCATAATCC | | | |
| DBLy6 | <i>IT4var20</i> | B/A | DC8 | FCR3/IT | TGCGATGTAGTTAACACCAC | GCACTCGCACCTTTCTAG | | | |
| DBLδ1 | <i>IT4var20</i> | B/A | no DC | FCR3/IT | TGTGATATAGAAAAACAC | ACATGGTTACAATATGTTTC | | | |
| CIDRβ1 | <i>IT4var20</i> | B/A | no DC | FCR3/IT | TCTAAAATTACAGTTAAATG | ACAGGGTTGCCACTAGCTTG | | | |
| DBLy12 | DBLδ5 | CIDRδ3 | DBLβ9 | <i>IT4var02</i> | A | DC5 | FCR3/IT | | Published in (31) |
| Recombinant Protein, in <i>E. coli</i> | Gene | Group | DC | gDNA origin | Primary Forward Primer (5'-3') | Primary Reverse Primer (5'-3') | | | |
| NTSB | DBLα2 | <i>IT4var19</i> | B/A | DC8 | FCR3/IT | GAAAACCTGTATTTCAGGGAAATGGGGCCCAAGGCCGC | TTTTCGAACTCGGGTGGCTCAAACAACTACACAAATCGGG | | |
| CIDRa1.1 | <i>IT4var19</i> | B/A | DC8 | FCR3/IT | GAAAACCTGTATTTCAGGGAGTAGTTGTTGTGAGGGT | TTTTCGAACTCGGGTGGCTCCATGCATCACCTTCAAATTA | | | |
| DBLβ12 | <i>IT4var19</i> | B/A | DC8 | FCR3/IT | GAAAACCTGTATTTCAGGGACCCAAAACTAAATAAACCCATG | TTTTCGAACTCGGGTGGCTCCATCCGCCGGTACTGGTGT | | | |
| DBLy6 | <i>IT4var19</i> | B/A | DC8 | FCR3/IT | GAAAACCTGTATTTCAGGGATGTTAAAATGGATGGAA | TTTTCGAACTCGGGTGGCTCCAACACTCACATTAGTTTC | | | |
| DBLδ1 | <i>IT4var19</i> | B/A | no DC | FCR3/IT | GAAAACCTGTATTTCAGGGATGCAAACCGTGGAAAGAA | TTTTCGAACTCGGGTGGCTCCAACATGGATTACAATTTC | | | |
| CIDRβ1 | <i>IT4var19</i> | B/A | no DC | FCR3/IT | GAAAACCTGTATTTCAGGGATCTGAATTAAAATAATTGTGAAA | TTTTCGAACTCGGGTGGCTCCAACAAGGTTTTGTCTCCGCACT | | | |
| DBLy9 | <i>IT4var19</i> | B/A | no DC | FCR3/IT | GAAAACCTGTATTTCAGGGATGCGAAATAGCGGAAGAAA | TTTTCGAACTCGGGTGGCTCCAACATTACACTTGTCTT | | | |
| CIDRa1.4 | <i>IT4var07</i> | A | DC13 | FCR3/IT | TAGAAAACCTGTATTTCAGGGACCCGACTGTGGAGTCATA | TTTTCGAACTCGGGTGGCTCAAACATGCTTCGTTGATT | | | |

Table S3. Binding of DC8 expressing parasites to endothelial cells

| Parasite line | FCR3 IT4VAR20* | FCR3 IT4VAR19a* | FCR3 IT4var06* | 3D7 PFD0020C* | 1965* | 1983* | FCR3 VAR2CSA* | FCR3 IT4VAR02* | FCR3 IT4VAR19b^ | FCR3 IT4VAR19b^ | FCR3 IT4VAR19b^ | FCR3 IT4VAR19b^ |
|---------------------|-------------------|--------------------|-------------------|------------------|------------------|------------------|---------------------|--------------------------|--------------------|---------------------------|--------------------|--------------------|
| Cell line | HBMEC (Brain) | HBMEC (Brain) | HBMEC (Brain) | HBMEC (Brain) | HBMEC (Brain) | HBMEC (Brain) | BeWo (Placental) | TrHBMEC (Bone marrow) | THBMEC (Brain) | CDC-BMEC (Bone marrow) | HCMEC (Heart) | HPMEC (Lung) |
| Medium | 100 ±9 | 100 ±7 | 100 ±10 | 100 ±5 | 100 ±9 | 100 ±17 | 100 ±16 | 100 ±12 | 100 ±26 | 100 ±20 | 100 ±37 | 100 ±45 |
| rEPCR | 12 ±1 | 25 ±4 | 12 ±0 | 47 ±1 | 37 ±1 | 30 ±3 | 108 ±12 | 94 ±14 | 34 ±18 | 34 ±24 | 36 ±12 | 46 ±25 |
| rICAM1 | 96 ±6 | 100 ±5 | nd | 114 ±16 | 130 ±11 | 123 ±11 | 108 ±14 | 104 ±8 | nd | nd | nd | nd |
| a-EPCR | 37 ±4 | 81 ±5 | 40 ±9 | 34 ±2 | 74 ±17 | 64 ±8 | nd | 103 ±2 | 48 ±23 | 66 ±14 | 49 ±21 | 50 ±37 |
| a-ICAM1 | 75 ±6 | 104 ±10 | 80 ±8 | 85 ±9 | 122 ±20 | 110 ±9 | nd | 110 ±2 | 172 ±43 | 107 ±39 | 88 ±36 | 81 ±46 |
| a-IT4VAR20 | 13 ±1 | 98 ±4 | nd | nd | nd | nd | 84 ±11 | 100 ±1 | | | | |
| a-CIDRa1.1_IT4VAR20 | 12 ±2 | 92 ±4 | 99 ±14 | 117 ±1 | nd | nd | 94 ±7 | 99 ±3 | | | | |
| a-DBLβ12_IT4var19 | 95 ±12 | 50 ±7 | 87 ±12 | nd | nd | nd | 79 ±2 | nd | | | | |
| a-DC5-IT4var02 | 103 ±9 | 90 ±4 | 93 ±11 | 91 ±12 | nd | nd | nd | 52 ±2 | | | | |
| a-IT4VAR13 | 92 ±28 | 97 ±3 | nd | 118 ±11 | nd | nd | 73 ±14 | 89 ±3 | | | | |
| a-VAR2CSA/a-PECAM1 | nd | nd | nd | nd | nd | nd | 6 ±1 | 26 ±3 | | | | |

*)EC binding characteristics of DC8/DC13-expressing parasite lines and two control lines (FCR3 VAR2CSA and FCR3 IT4VAR02) measured as 3H-hypozanthine marked and EC bound infected erythrocytes after washing with pipetting robot. Results are mean ± s.d. of triplicate measurements in one representative experiment of at least three. *Var/PfEMP1* expression profiles are given in Fig. S3.

^) Binding of IT4VAR19 (DC8)-expressing parasites to endothelial cells originating from different tissues; Brain: Transformed human brain microvascular endothelial cells (THBMEC); bonemarrow endothelial cells (CDC-BMEC); heart: Human cardiac microvascular endothelial cells (HCMEC); Lung: pulmonary microvascular endothelial cells (HPMEC). Binding was determined as adhering infected erythrocytes per endothelial cell by counting under 400X magnification. Binding is shown as average ± s.d. of at least two experiments and in relation to binding in medium.

Table S4 Data pertaining to the clinical parasite isolates tested for EPCR binding

| | | Severe malaria* (N=15) | Uncomplicated malaria* (N=5) | Mild malaria* (N=10) |
|---|--|---------------------------|---------------------------------|------------------------------|
| Clinical characteristics | | | | |
| Age | Mean (min,max) years | 2.5 (0.9;4.9) | 2.3 (0.6;4.6) | 9.3 (4.3;16.4) |
| Blantyre coma score | Mean (min,max) | 1.5 (0;5) | 5 (5;5) | 5 (5;5) |
| Haemoglobin | Mean (min,max) g/dl | 6.0 (3.4;10.5) | 9 (8.2;9.9) | 12.5 (9.9;14.1) |
| Parasite density | Mean (min,max) parasites/ul | 148,157 (20,825;313,740) | 43,498 (5,670;79,940) | 12,440 (1,428;34,680) |
| Culture [^] | Mean (min,max) days | 17.5 (4;21) | 19.8 (8;29) | 17.6 (12;22) |
| Var gene transcript analysis[¤] | | | | |
| <i>Primer name</i> | | <i>Primer target</i> | | |
| DBL α 1 not var3 | group A <i>var</i> genes | 6 (4;8) | 1 (1;1) P=0.0024 [§] | 1 (1;3) P=0.048 [#] |
| DBL α 2/a1.1/2/4/7** | Group A <i>var</i> genes w/ CIDR α 1 | 5 (3;11) | 1 (1;1) P=0.0086 [§] | 1 (1;2) P=0.005 [#] |
| B1 | group B <i>var</i> genes | 1 (1;3) | 2 (1;2) P=0.95 [§] | 3 (2;3) P=0.075 [#] |
| C1 | group C <i>var</i> genes | 1 (1;5) | 2 (2;3) P=0.63 [§] | 1 (1;2) P=0.34 [#] |
| CIDR α 1.1 | DC8 <i>var</i> genes | 5 (1;14) | 1 (1;1) P=0.061 [§] | 1 (1;1) P=0.020 [#] |
| CIDR α d | DC16 group A <i>var</i> genes | 1 (1;1) | 1 (1;1) P=0.20 [§] | 1 (1;1) P=0.15 [#] |
| CIDR α 2.2 | subset of group B <i>var</i> genes | 1 (1;2) | 1 (1;8) P=0.66 [§] | 1 (1;1) P=0.091 [#] |

* Patients with severe malaria and uncomplicated malaria were admitted to Korogwe District Hospital, Tanzania. Severe malaria patients had cerebral malaria (Blantyre Coma Score<3) and/or severe anaemia (haemoglobin<5g/dl). Patients with uncomplicated malaria were selected among the admitted patients who were fully conscious (Blantyre Coma Score=5) and a haemoglobin>8g/dl. Patients with mild malaria were largely asymptomatic and recruited during village surveys

[^]Number of days in culture before assay.

[¤] Quantitative PCR assay performed with previously published³ *var* typing primers at the time of parasite binding assay (results shown as Median transcript units (25% & 75% percentiles) showing that DC8 and group A (incl. DC13) encoding *var* genes are transcribed at higher levels in severe malaria parasite isolates than isolates from patients with mild or uncomplicated malaria.

[§] Wilcoxon rank sum test for comparison between parasites from patients with severe or uncomplicated malaria.

[#] Wilcoxon rank sum test for comparison between parasites from patients with severe or mild malaria.

**The primer "DBL α 2/a1.1/2/4/7" was designed and validated to target the subset of DBL α sequences flanked by CIDR α 1 domains incl. genes encoding DC8, DC13 and DC15.

Figure S1

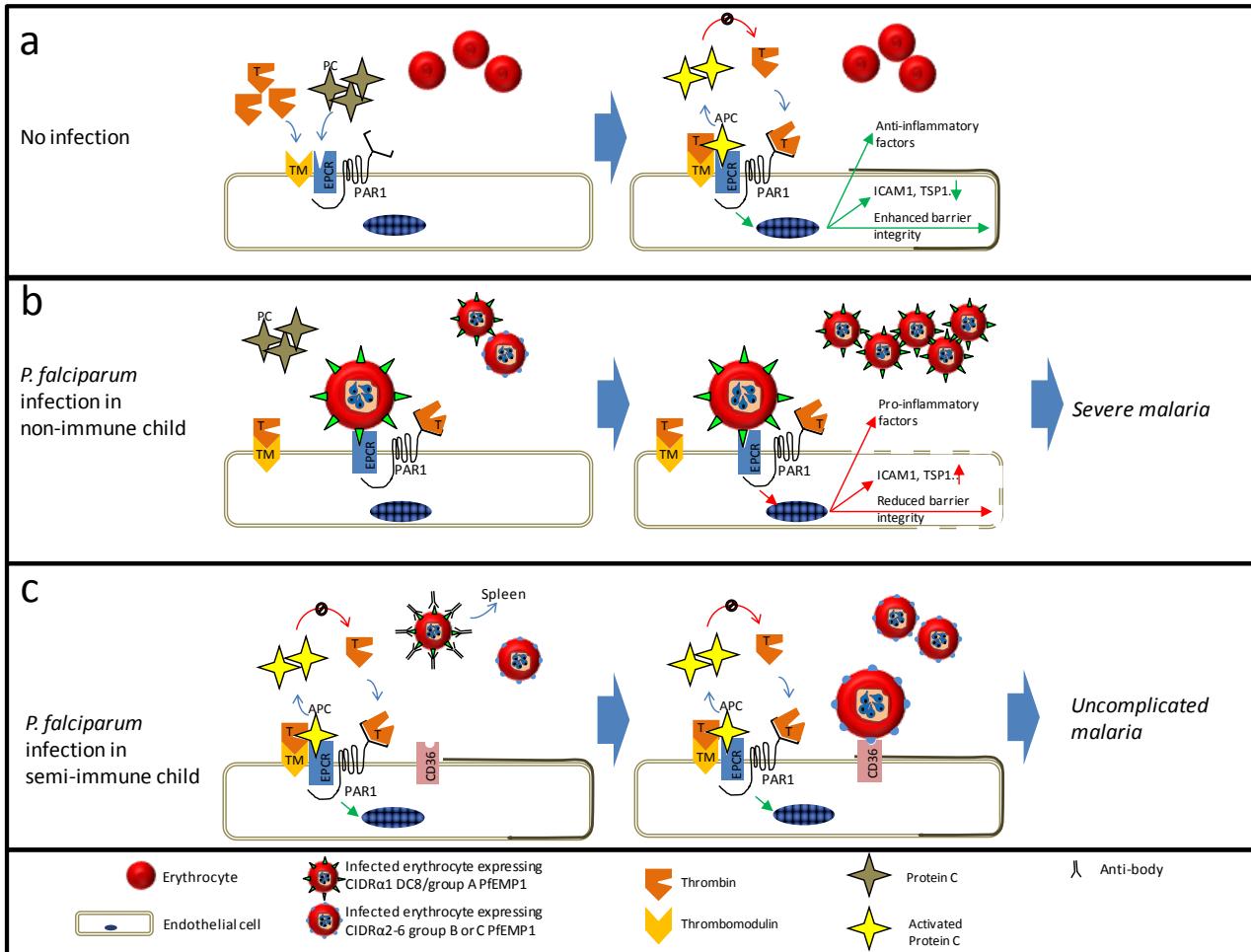


Figure S1. Model of EPCR-mediated parasite binding to endothelial cells leading to severe malaria

- a) In healthy non-infected infected individuals, the thrombin and thrombomodulin complex activates PC bound to EPCR to form APC. The APC/EPCR complex induces PAR1 signalling promoting anti-inflammatory and cytoprotective (enhanced endothelium barrier integrity) effects. APC released into plasma attenuates thrombin production.
- b) In *P. falciparum* infected non-immune children, parasites expressing CIDR α 1 containing DC8/group A PfEMP1 bind EPCR. This leads to locally reduced impact of APC/EPCR on PAR1, and increased thrombin-induced PAR1 signalling causing general pro-inflammatory effects, reduced barrier integrity and increased endothelial membrane presentation of other receptors (e.g ICAM-1 and TSP1) known to promote parasite sequestration.
- c) In *P. falciparum* infected semi-immune children antibodies have been acquired to DC8 and group A PfEMP1 variants early in life. These antibodies inhibit PfEMP1:EPCR mediated parasite sequestration and send DC8/group A PfEMP1 expressing parasites to destruction in the spleen, leaving parasite sequestration depended on PfEMP1 variants with affinity for the less detrimental CD36 interaction.

Figure S2

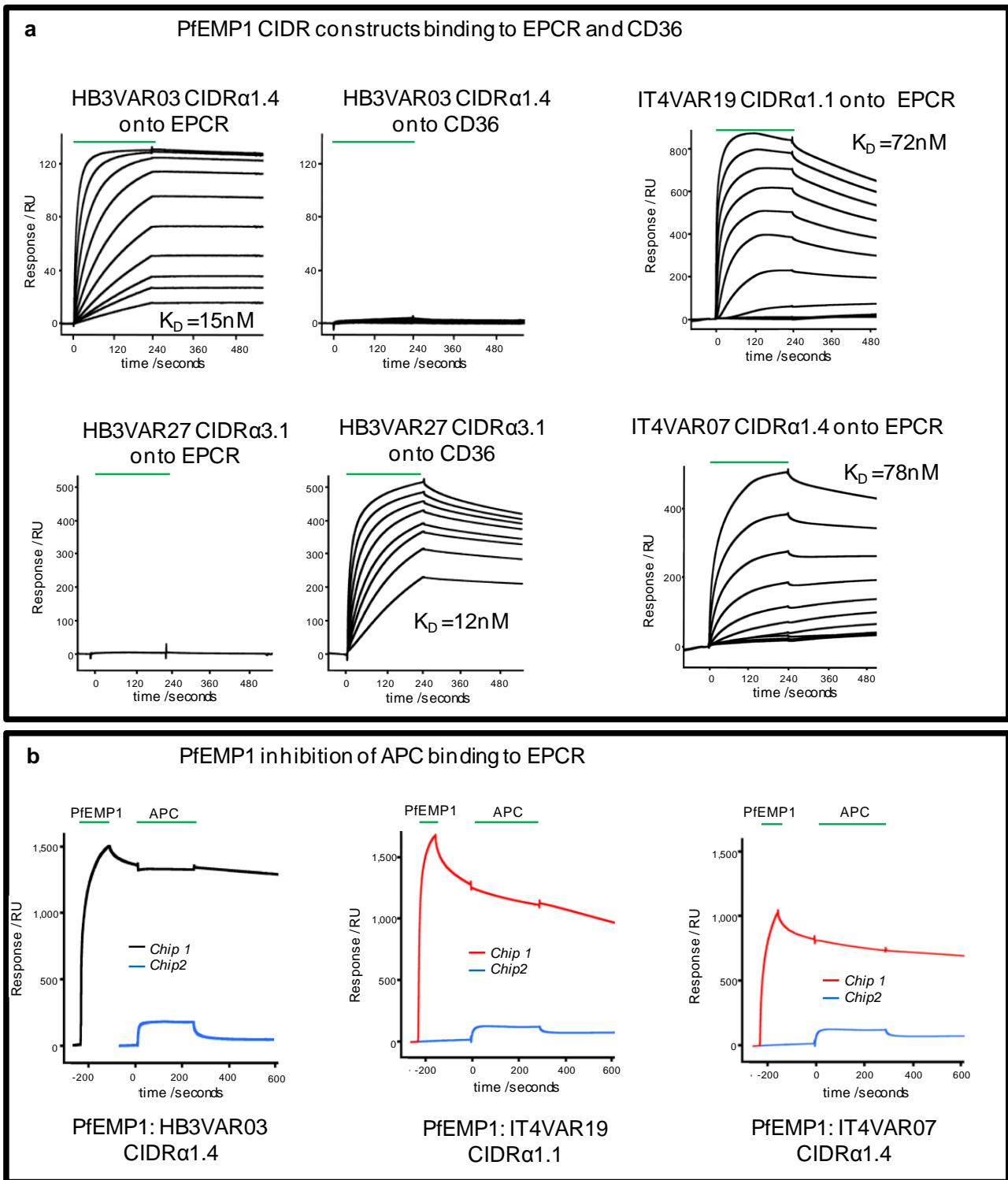


Figure S2. Additional SPR sensorgrams

a) SPR sensorgrams of recombinant PfEMP1 protein binding to EPCR and CD36. Binding was tested in two-fold dilutions of PfEMP1 from 0.25 μM for HB3var27, 0.5 μM for HB3var03 and IT4var07 and 2 μM for the rest. Protein infusion times marked by green lines. CIDR α 1.1 of DC8 and CIDR α 1.4 of DC13 bind EPCR, but not CD36, with high affinity, whereas a group B CIDR α 3.1 binds CD36, but not EPCR, with high affinity.

b) Sensorgrams showing binding competition of PfEMP1 and APC to EPCR. In each case, proteins are at 2 μ M concentration. Each panel show sensorgrams for two chips coated with EPCR. Red curve: EPCR coated chip 1 sequentially flushed with recombinant antigen, buffer, APC and buffer. Blue curve: EPCR coated chip 2 flushed with APC only. The lack of binding response upon addition and removal of APC flow to the PfEMP1 pre-incubated EPCR coated chip compared to the APC binding response to the EPCR coated chip alone, shows that PfEMP1 obstruct APC binding to EPCR.

Figure S3

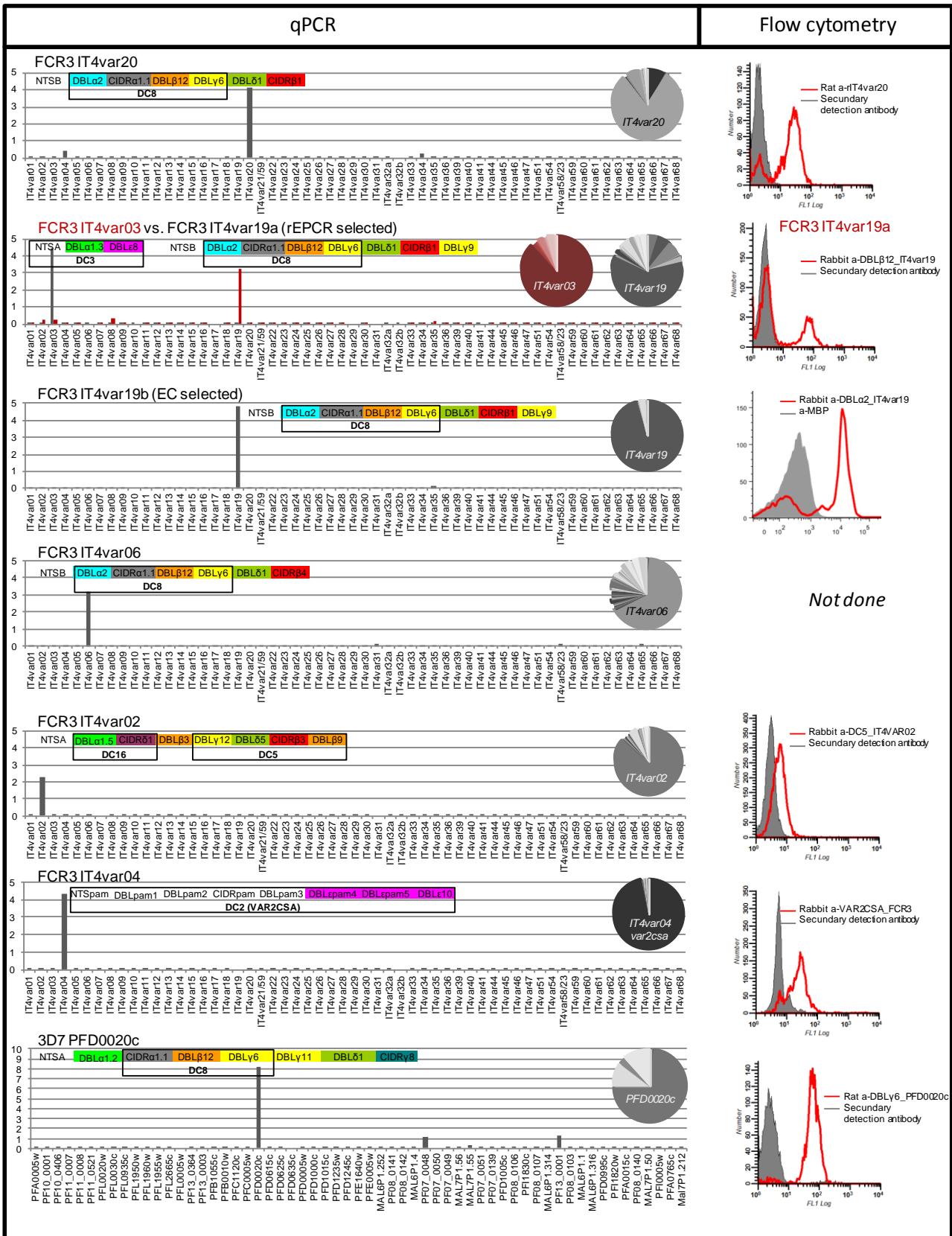


Figure S3. Var/PfEMP1 expression profiles of FCR3/IT and 3D7 parasite lines

The *var* transcript profile of investigated parasite lines is shown in bar charts as transcript levels of

each *var* gene of the FCR3/IT or 3D7 genomes, relative to the averaged transcript level of two control genes (*seryl-tRNA synthetase* (PF07_0073) and *aldolase* (PF14_0425). The *var* transcript distribution in the tested parasite lines are also shown as pie charts. The domain and DC composition of the dominantly expressed PfEMP1s are shown. The PfEMP1 erythrocyte surface expression of the dominantly expressed PfEMP1 was verified by flow cytometry (charts) using antibodies raised to homologous recombinant PfEMP1 domains (red lines) vs. secondary negative control antibodies (grey area plot).

Figure S4

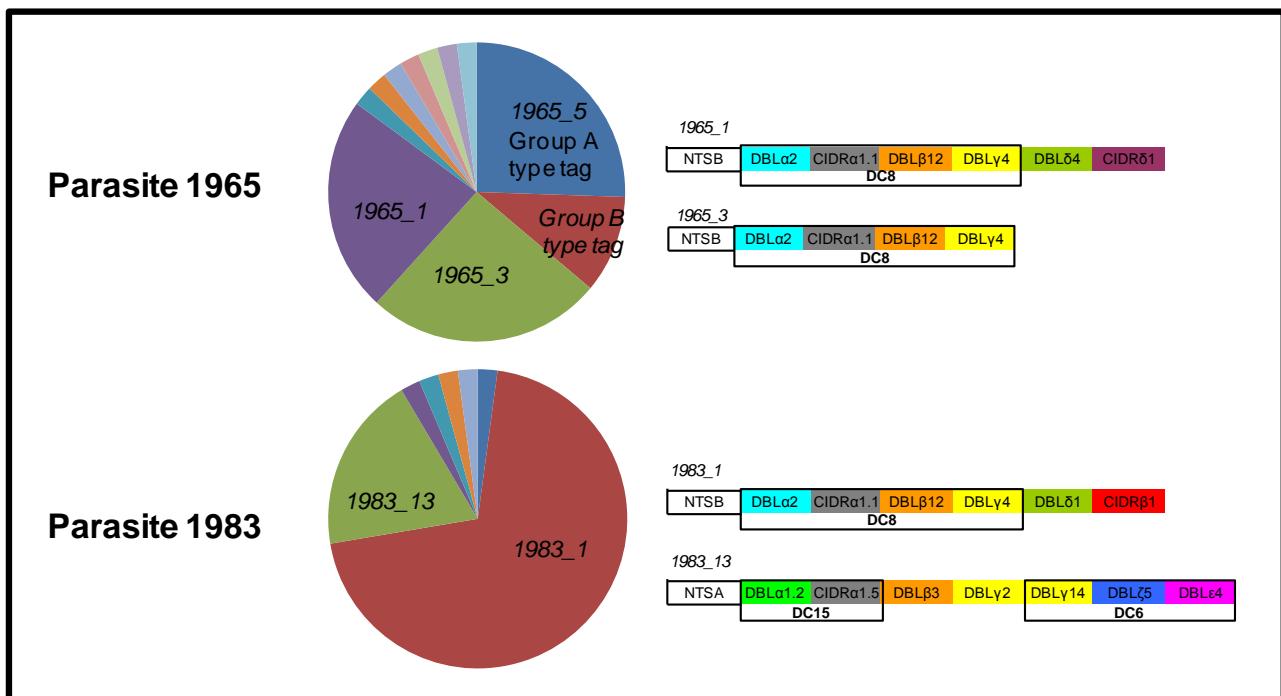


Figure S4. *Var* expression profiles of parasite isolates 1965 and 1983

Distribution of unique *var* DBL α tags (pie charts) showed that both parasite lines expressed predominantly DC8 encoding *var* genes (annotated) also previously identified as highly expressed in the *ex vivo* patient samples ³.

Figure S5

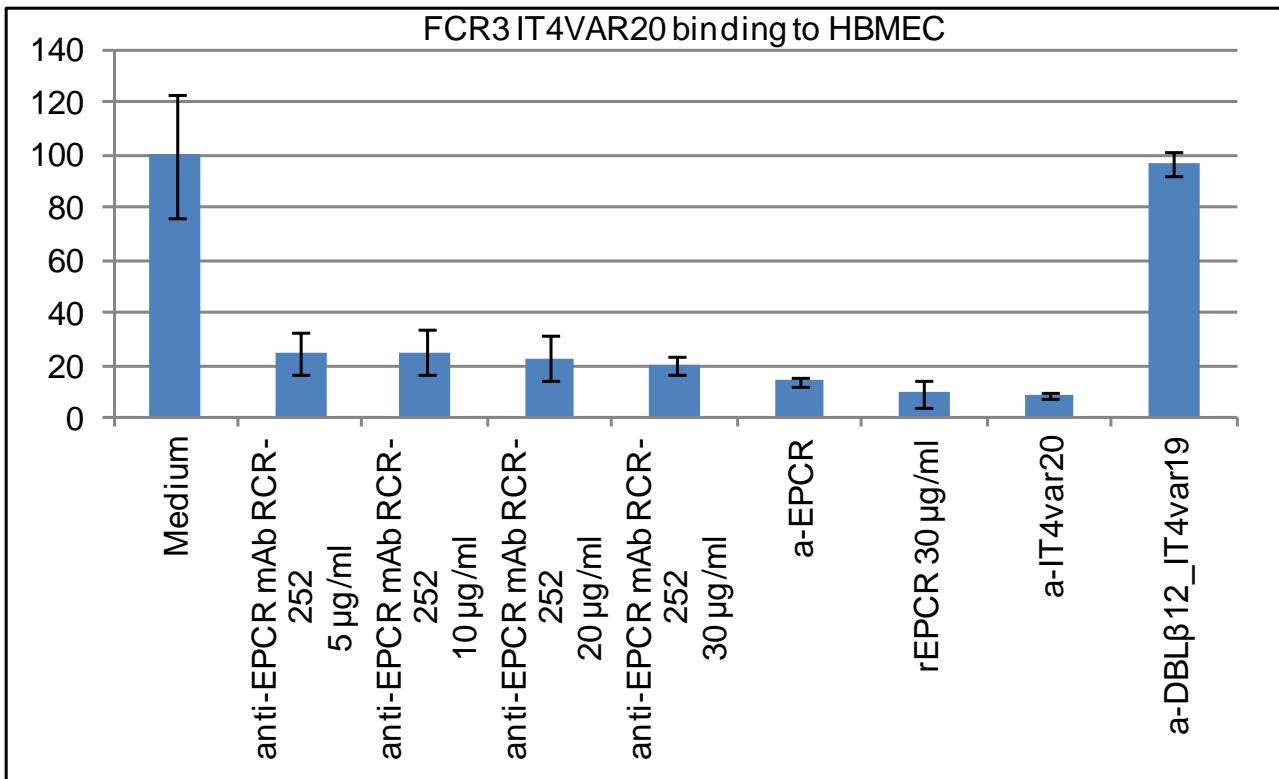


Figure S5. Effect of anti EPCR monoclonal antibody RCR-252 on FCR3 IT4VAR20 parasite binding to brain endothelial cells. Binding level of the FCR3/IT IT4VAR20 parasite line to human brain microvascular endothelial cells (HBMEC) was measured as scintillation counts of ^3H -hypoxanthine labeled infected erythrocytes bound to endothelial cells after washing with pipetting robot. Binding levels are given as mean of three technical triplicates \pm s.d. in relation to binding to HBMEC in medium set to 100%. The RCR-252 is known to inhibit APC binding to EPCR. This shows that the binding of DC8 expressing parasites to brain endothelial cells is mediated by PfEMP1 interacting with EPCR at or close to the binding site of RCR-252, and suggests that PfEMP1 bind EPCR near or at the same region as APC. Polyclonal anti-EPCR antibodies (a-EPCR), purified rat anti full-length recombinant IT4VAR20 IgG antibodies (a-IT4VAR20); and rabbit anti-IT4var19 DBL β 12 antibodies.

Figure S6

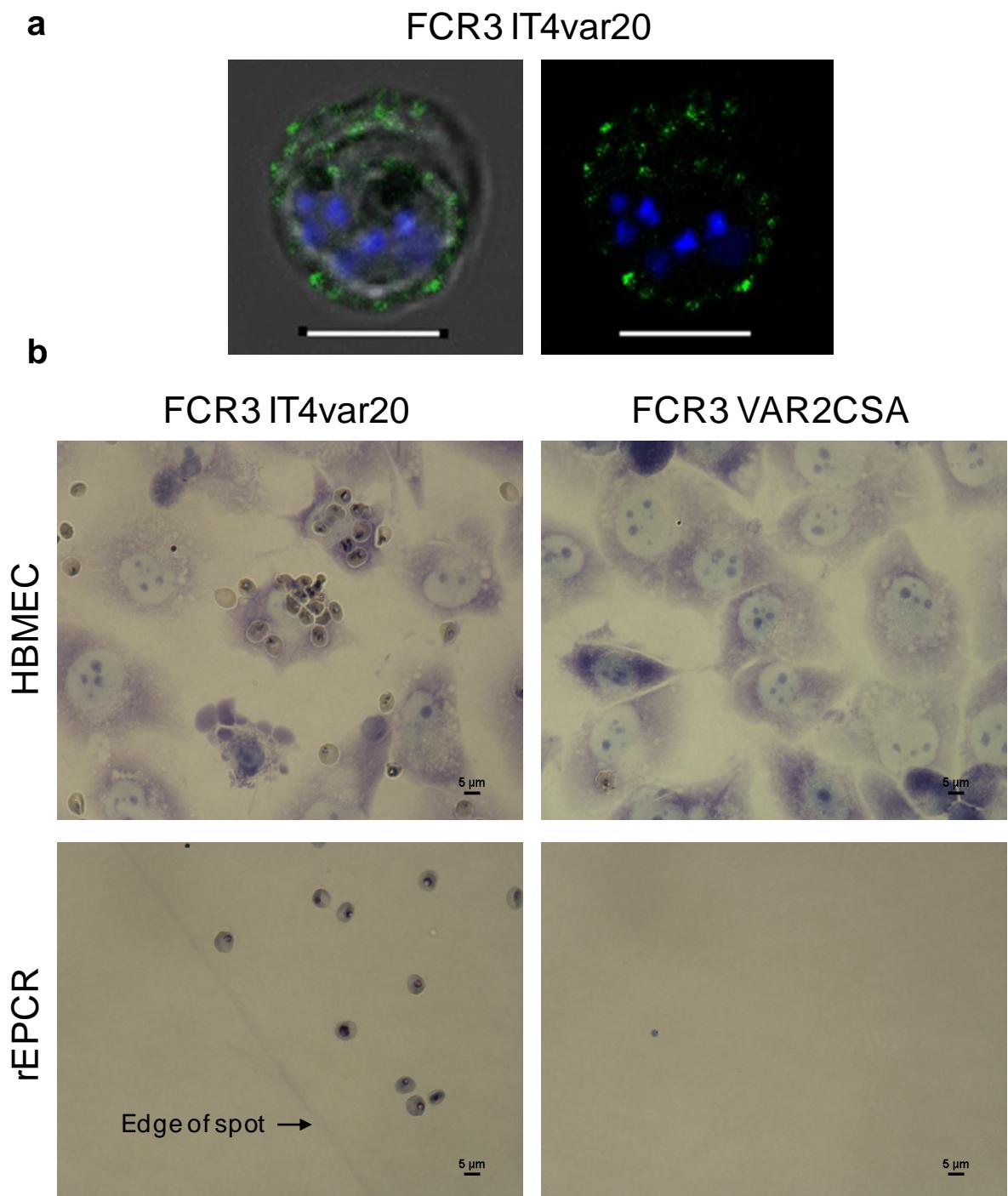


Figure S6. Microscopy pictures of PfEMP1 expression and infected erythrocyte binding
a) Live parasites of the FCR3 IT4VAR20 line were stained with rat anti-rIT4VAR20 antibodies (green) and nuclei were stained with DAPI (blue). A DIC shadow-cast image with the fluorescence image superimposed (first picture) and the fluorescence image alone (second picture) on a serorepresentative infected erythrocyte are shown. Scale bar 5 μ M.

b) FCR3 IT4VAR20 and FCR3 VAR2CSA parasites binding human brain microvascular endothelial cells (HBMEC) or Petri dish spotted with recombinant human EPCR.